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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,622	02/13/2002	Raymond L. Houghton	210121.470C11	2478

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SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 6300
SEATTLE, WA 98104-7092

EXAMINER	
EPPS, JANET L	

ART UNIT	PAPER NUMBER
1635	10

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,622	HOUGHTON ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- Th MAILING DATE of this communication app ars on th cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group V, claims 8-9, in Paper No. 9 is acknowledged. However, Applicants have cancelled the claims drawn to the elected invention and have added new claim 11.

Claim Rejections - 35 USC § 112

2. Claim 11 is rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility due to its not being supported by either a credible, specific or substantial utility or a well established utility.

The instant claim is drawn to a method for stimulating an immune response in a patient, comprising administering to the patient a composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from a polypeptide sequence comprising SEQ ID NO: 475; and sequences having at least 90% identity to the sequence set forth in SEQ ID NO: 475.

The specification as filed (3rd paragraph page 110) indicates that the utility for the instantly claimed method for stimulating an immune response in a patient comprising administering compositions comprising the polypeptides of the present invention, reads on a method of immunotherapy for the treatment of breast cancer. This immunotherapy relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response modifying agents such as the polypeptides of the present invention (bridging paragraph of pages 110-111). However, the asserted utility of the claimed

method using the polypeptide according to SEQ ID NO: 475, or sequences having at least 90% to SEQ ID NO: 475 is neither specific, substantial or credible.

First, it is noted that the asserted use of the polypeptide according to SEQ ID NO: 475 for diagnostic or therapeutic purposes, is neither substantial nor specific due to being generic in nature and applicable to a myriad of such compounds. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the polypeptide according to SEQ ID NO: 475, such that another non-asserted utility would be well established for the compound.

In regards to the credibility of the asserted utility of the claimed polypeptide, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. [See the Utility Guidelines; Federal Register, Vol. 66, No. 4, January 5, 2001]

In the instant case, the specification (page 125, lines 22-24) as filed states that the sequence according to SEQ ID NO: 475 represents the amino acid sequence of an alternative splice form of B726P. However, there is no evidence provided in the specification as filed that would indicate that this polypeptide actually functions as a breast tumor antigen, and there is no indication that the expression of this polypeptide is over expressed in breast tumor cells at least

two fold or five fold greater level of expression than in normal cells (See utility statement 3rd paragraph, page 39). The specification as filed clearly states that the polypeptide according to SEQ ID NO: 475 is not the breast tumor antigen according to B726P of the present invention, but actually is encoded by an alternative splice form of the B726P mRNA. However, it is unclear if the sequence according to SEQ ID NO: 475 represents a polypeptide that is normally expressed in breast tumor tissue, or further that the abundance of this polypeptide is somehow over-expressed in breast tumor tissue, wherein the increased abundance of this polypeptide correlates with the presence of disease in breast tissue.

Additionally, in regards to the immunotherapeutic use of the claimed method comprising the administration of a polypeptide comprising a sequence according to SEQ ID NO: 475 or sequences having at least 90% identity to this sequence, the specification as filed does not provide adequate guidance and/or instruction that would allow one of skill in the art to practice a therapeutic method comprising the administration of a composition comprising said polypeptide or variants thereof comprising at least 90% identity. First, if a polypeptide according to SEQ ID NO: 475 was over-expressed in breast tumor tissue, it is unclear how administering a composition comprising said polypeptide would be "therapeutic" or effective to alleviate a condition associated with the over-expression of said polypeptide. Even if an immune response was triggered by the administration of the polypeptide, in situations where the polypeptide is over-expressed it is unclear how the addition of more polypeptide would be sufficient to stimulate any noticeable additional immune response for treatment purposes. Moreover, since it is uncertain that a polypeptide comprising a sequence according to SEQ ID NO: 475 is normally

expressed at detectable levels in breast tissue, it is unclear what potential toxic effects may occur once administered to a patient.

Moreover, since applicants have not provided any direct evidence demonstrating a direct correlation between the over-expression of the nucleic acid encoding the polypeptides of the present invention in breast tumor tissue, and the level of polypeptide present in the diseased breast tissue. One of skill in the art would not accept on its face that the mRNA expression level in a cell is immediately correlative or even representative of the level of polypeptide produced in said cell. See Anderson et al. (*Electrophoresis* 1997, Vol. 18, pages 533-537), which addresses the extent to which mRNA abundances are predictive of protein abundances. In regards to the human liver, Anderson et al. teach "[A] correlation coefficient of 0.48 was obtained between the mRNA and protein abundances determined.....suggesting that post-transcriptional regulation of gene expression is a frequent phenomenon in higher organism." (See Abstract). In one specific example, Anderson et al. show in the comparison of the β and γ actins "persuasive evidence of post-transcriptional regulation," wherein the two proteins are essentially identical in function but have "mRNA-to-protein ratios differing by more than a factor of two between the two genes (page 536, bridging paragraph)." Additionally, Anderson et al. concludes: "[H]ence it appears likely that of the total protein abundances is significantly different from that of mRNAs,...and that techniques able to detect down to a specified percent abundance threshold would reveal more proteins at a given threshold than mRNAs." (Discussion, page 537, last paragraph)

Based upon the observations made by Anderson et al., the prior art at does not provide adequate support for Applicant's direct correlation between the abundance of the mRNA transcript in breast-tumor tissue and the relative abundance of the polypeptide expression in this

same tissue. Therefore, Applicant's asserted utility of the polypeptide according to SEQ ID NO: 475 for diagnosis or monitoring of breast cancer is neither specific, substantial, or credible.

It is noted that during the prosecution of parent application 09/604,287, Applicants provided evidence of patentable utility by way of a declaration submitted under 37 CFR 1.131 and 37 CFR 1.132. However, declarations filed during the prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit or declaration, the applicant should make the remarks of record in the later application and include a copy of the original affidavit or declaration filed in the parent application.

3. Claim 11 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

4. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claim reads on an isolated polypeptide having at least 90% identity to SEQ ID NO: 475. The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus of isolated polypeptides having at least 90% identity to SEQ ID NO: 475. Neither the specification as filed, nor the claims place any limit on the size of the

claimed polypeptides, the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the claim polypeptides, it is only required that the isolated polypeptide comprises at least 90% identity SEQ ID NO: 475. Thus, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between the genus members are permitted, and neither the specification nor the claims provide any guidance as to what specific changes should be made.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein sequence. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a known sequence (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in under-predictions of functionality of a new protein and (2) over-predictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity.

Due to the limited structural information regarding what amino acid residues that may be deleted, substituted or inserted into the polypeptides according to the present invention, wherein said polypeptide retains at least 90% identity to SEQ ID NO: 475 and maintains the ability to be used to stimulate an immune response in a patient, the level of unpredictability associated with

protein structure and predicting protein function, and the lack of guidance thereof in the specification as filed, it is concluded that Applicant's disclosure is insufficient to adequately describe the genus of polypeptides encompassed by the claimed invention. Applicant's specification does not provide sufficient description for the broad genus of polypeptides encompassed by the instant claims since providing a means to isolate a compound cannot show possession. What is required is an actual description of the claimed invention, particularly by means of drawings or structural chemical formulas that show that the invention was complete at the time of filing of the claimed invention.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is required. Since the disclosure fails to describe the common attributes or characteristics that identify the members of the genus, and because the genus is highly variant, the disclosed sequence of SEQ ID NO: 475, alone is not sufficient to describe claimed genus.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
March 5, 2003